ORIGINAL ARTICLE

Alteplase for Posterior Circulation Ischemic Stroke at 4.5 to 24 Hours

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ABSTRACT

BACKGROUND

The effects and risks of the use of intravenous thrombolysis between 4.5 and 24 hours after the onset of a posterior circulation ischemic stroke are not well studied.

METHODS

In a trial conducted in China, we randomly assigned patients with posterior circulation stroke, without extensive early hypodensity on computed tomography and with no planned thrombectomy, to receive alteplase (0.9 mg per kilogram of body weight; maximum dose, 90 mg) or standard medical treatment 4.5 to 24 hours after the onset of symptoms. The primary outcome was functional independence (defined as a score of 0 to 2 on the modified Rankin scale; scores range from 0 to 6, with higher scores indicating greater disability) at 90 days. The key safety outcomes were symptomatic intracranial hemorrhage and death.

RESULTS

A total of 234 patients were enrolled; 117 were assigned to the alteplase group and 117 to the standard treatment group. The median score on the National Institutes of Health Stroke Scale was 3 (interquartile range, 2 to 6) (scores range from 0 to 42, with higher scores indicating greater neurologic deficit). A higher percentage of patients in the alteplase group than in the standard treatment group had functional independence at 90 days (89.6% vs. 72.6%; adjusted risk ratio, 1.16; 95% confidence interval [CI], 1.03 to 1.30; P=0.01). The incidence of symptomatic intracranial hemorrhage within 36 hours was 1.7% in the alteplase group and 0.9% in the standard treatment group. At 90 days, 5.2% of the patients in the alteplase group and 8.5% of those in the standard treatment group had died.

CONCLUSIONS

Among Chinese patients with mainly mild posterior circulation stroke who did not receive thrombectomy, alteplase administered 4.5 to 24 hours after stroke onset resulted in a higher frequency of functional independence at 90 days than standard medical care. (Funded by the National Natural Science Foundation of China; EXPECTS ClinicalTrials.gov number, NCT05429476.)

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*A full list of the EXPECTS Group members is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Intravenous thrombolysis (IVT) administered within 4.5 hours after the onset of ischemic stroke is standard care for eligible patients.[1] Endovascular thrombectomy is also standard care, but IVT is used when endovascular thrombectomy is not available. Alteplase administered up to 9 hours after the onset of stroke has been shown to be effective in patients with salvageable brain tissue identified with the use of computed tomography (CT) perfusion or perfusion–diffusion magnetic resonance imaging (MRI).[2,3] Two recent randomized controlled trials have explored the possibility of extending the treatment window for IVT to 24 hours after onset in patients with large-vessel occlusion of the anterior circulation identified with the use of perfusion imaging techniques.[4,5]

Whether the therapeutic window for IVT can be extended in patients with posterior circulation stroke has not been adequately studied. Atypical symptoms in the posterior circulation are often complex and variable,[6] leading to misdiagnosis or delayed diagnosis and limiting research in emergency settings, while perfusion imaging in the posterior circulation remains challenging with no validated protocols to extend the treatment window. It has been suggested that the anatomical and pathophysiological features of the brain stem and cerebellum, which are supplied by the perforating branches of the basilar artery, may render these areas more resistant to ischemia.[7] The risk of intracranial hemorrhage after IVT is notably lower in strokes involving the posterior circulation than in those involving the anterior circulation,[8] which suggests that the therapeutic window for thrombolytic therapy could be extended in patients with posterior circulation strokes.

Recent trials have shown the effectiveness of thrombectomy in treating basilar-artery occlusion.[9,10] However, endovascular therapy is not always available because of technical limitations, insufficient resources, and high costs. Furthermore, posterior circulation strokes, even without large-vessel occlusion, can result in poor outcomes.[11] The Extending the Time Window for Thrombolysis in Posterior Circulation Stroke without Early CT Signs (EXPECTS) trial was designed to assess whether alteplase administered 4.5 to 24 hours after stroke onset could benefit patients with posterior circulation stroke who did not have endovascular thrombectomy planned. We aimed to explore the potential for extending the window of thrombolysis without perfusion imaging guidance, given the lower risk of hemorrhage in the posterior circulation.

Methods

A Quick Take is available at NEJM.org

Trial Design and Oversight

We conducted a prospective, multicenter, open-label, randomized trial with blinded outcome assessment at 30 stroke centers in China (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We recruited patients with acute posterior circulation ischemic stroke, without extensive early hypodensity on CT, who had had symptom onset 4.5 to 24 hours before screening. For patients with unwitnessed strokes and stroke symptoms present on awakening, the onset time was estimated as the midpoint of the time between when the patient was last known to be well and when the patient was found to have symptoms. Details regarding the trial rationale, design, and methods are provided in the protocol (available at NEJM.org). The steering committee oversaw the design and execution of the trial as well as the analysis of the data, and a data and safety monitoring board performed regular safety assessments. At the time of the database lock, the last author had full access to the data and affirms the adherence of the trial to the protocol, as well as the integrity, completeness, and precision of the reported outcomes and adverse events. The trial funder (National Natural Science Foundation of China) did not participate in the conduct of the trial.

The trial protocol was approved by the institutional review board at the Second Affiliated Hospital of Zhejiang University, School of Medicine, and at each participating trial site. The statistical analysis plan is available with the protocol. The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice.[12] Written informed consent was obtained from all the patients or their representatives before enrollment.

Patients

Eligible patients were 18 years of age or older and had clinical signs of posterior circulation

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stroke with either confirmation on diffusion-weighted MRI or lack of an alternative diagnosis on CT. Although not mandated, symptomatic stenosis or occlusion of a posterior circulation artery on CT angiography or evidence of hypoperfusion on CT perfusion imaging could be used to support the diagnosis. Eligible patients had onset of stroke 4.5 to 24 hours before randomization, a posterior circulation Acute Stroke Prognosis Early CT Score (PC-ASPECTS; scores range from 0 to 10, with lower scores indicating more extensive infarction in the posterior circulation) of 7 or higher (patients were eligible if the PC-ASPECTS on diffusion-weighted imaging was <7 but the PC-ASPECTS on noncontrast CT was ≥7),[13] a score of 1 or higher on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater neurologic deficit), and a prestroke score of 0 or 1 on the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability). The imaging training and evaluation protocol for PC-ASPECTS is provided in the Supplementary Appendix.

Patients were ineligible if endovascular treatment was planned at the time of randomization or if guideline-based contraindications for alteplase other than the time window were present. Additional information regarding inclusion and exclusion criteria is provided in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS

Randomization was performed by investigators at each trial site with the use of a secure, central online system. Eligible patients were randomly assigned in a 1:1 ratio to receive either alteplase or standard medical treatment. A minimization process was used to balance the two groups, with stratification according to age (<65 years or ≥65 years), time from symptom onset to randomization (<9 hours or ≥9 hours), and NIHSS score at randomization (<10 or ≥10).

Patients in the alteplase group received intravenous alteplase at a dose of 0.9 mg per kilogram of body weight (maximum dose, 90 mg), with 10% of the total dose administered as a bolus over 1 minute, followed by an infusion of the remaining 90% over 60 minutes. Patients in the standard treatment group received antiplatelet therapy and other treatments in accordance with the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018. Patients who had endovascular thrombectomy planned during the screening phase were excluded from the trial, but the protocol allowed for rescue thrombectomy. Patients who received rescue thrombectomy were included in the intention-to-treat analysis but were omitted from the per-protocol analysis.

OUTCOMES

The primary outcome was functional independence (defined as a score of 0 to 2 on the modified Rankin scale) at 90 days. Secondary outcomes included the ordinal distribution of the scores on the modified Rankin scale at 90 days, absence of disability (a score of 0 or 1 on the modified Rankin scale) at 90 days, and major neurologic improvement (defined as a reduction of ≥8 points on the NIHSS or an NIHSS score of ≤1) at 24 hours and at 7 days. Safety outcomes included symptomatic intracranial hemorrhage (defined as any intracranial hemorrhage associated with a worsening [i.e., increase] of ≥4 points on the NIHSS or leading to death that was identified as the predominant cause of neurologic deterioration) within 36 hours after randomization,[14] parenchymal hematoma within 36 hours after randomization, any intracranial hemorrhage within 36 hours after randomization,[15] and death from any cause within 90 days.

Primary outcome assessments were conducted by trained third-party personnel (who were unaware of the trial-group assignments) during standardized in-person visits or through telephone calls. Data on demographic characteristics, medical history, current medications, laboratory findings, neurologic function (assessed with the use of the modified Rankin scale and NIHSS), and imaging results were collected at screening. CT or MRI was performed at baseline to confirm eligibility. Hemorrhagic transformation was evaluated with the use of CT or MRI between 24 and 36 hours after randomization. Adverse events were documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

The primary analysis was performed in the full trial population on an intention-to-treat basis and included all the patients who had undergone randomization and for whom outcomes could be

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assessed. The safety analysis included all the patients who had undergone randomization and had received trial treatment and undergone at least one assessment of safety outcomes.

We compared the primary, secondary, and safety outcomes between the treatment groups. The effects of alteplase as compared with standard medical treatment are reported as risk ratios with 95% confidence intervals. For the primary efficacy outcome, comparisons between treatment groups were adjusted according to age (<65 years or ≥65 years), NIHSS score at randomization (<10 or ≥10), and time from stroke onset to randomization (<9 hours or ≥9 hours), with results presented as adjusted risk ratios with corresponding 95% confidence intervals. The shift in scores on the modified Rankin scale toward better functional outcomes was estimated with the use of an ordinal logistic model, with a common odds ratio and 95% confidence interval being derived after confirmation that the proportional-odds assumption had been satisfied. Because there was no plan to adjust the widths of the 95% confidence intervals for multiplicity, no definitive conclusions can be drawn from these data. The statistical analysis plan required multiple imputation for missing primary outcome data.

Prespecified subgroups were categorized according to age (<65 years or ≥65 years), sex, NIHSS score at randomization (<10 or ≥10), time from stroke onset to randomization (>4.5 to <9 hours, 9 to 24 hours, or unknown onset time), PC-ASPECTS at randomization (<9 or ≥9), type of imaging evaluation before randomization, and stroke classification. Post hoc analyses of functional outcomes were performed with the use of logistic regression, with adjustment for age, NIHSS score at randomization, and time from stroke onset to randomization.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). Adjusted risk ratios were calculated with the use of a log-binomial regression model.

RESULTS

PATIENTS

From August 2022 through May 2024, a total of 234 patients underwent randomization; 117 patients were assigned to receive alteplase, and 117 were assigned to receive standard medical treatment. Details regarding exclusion criteria and protocol violations are provided in Figure S2. A total of 2 patients were lost to follow-up, 2 patients in the standard treatment group crossed over to receive alteplase, and 9 patients in the alteplase group crossed over to standard treatment. Rescue thrombectomy was performed in 4 patients in the alteplase group and in 7 in the standard treatment group.

The characteristics of the patients at baseline were mostly balanced between the two groups and were generally representative of the expected patient population, with the exception of stroke classification (Table 1 and Tables S1 and S2). A total of 27 patients had cardioembolism, 75 had large-artery atherosclerosis (64 intracranial atherosclerosis and 11 extracranial atherosclerosis), 95 had small-vessel occlusions, and 37 had strokes of undetermined or other cause. A greater number of small-vessel occlusions was observed in the alteplase group than in the standard treatment group. Among the 124 patients who received standard treatment, 54 (43.5%) were receiving mono-antiplatelet therapy, 70 (56.5%) were receiving dual-antiplatelet therapy, and all were receiving statins. The median age was 64 years (interquartile range, 55 to 74), and 34.6% of the patients were women. Randomization occurred at a median of 564 minutes after symptom onset (interquartile range, 390 to 834). The median NIHSS score at randomization was 3 (interquartile range, 2 to 6), indicating that most patients had mild strokes.

A total of 144 patients (61.5%) were enrolled with confirmation of posterior circulation ischemic stroke on MRI. Among the remaining patients, 17 (7.3%) had diagnoses supported by findings on CT angiography or CT perfusion, while 73 (31.2%) were enrolled solely on the basis of clinical presentation and noncontrast CT findings. Among these 73 patients, 3 patients had no definitive infarction shown on follow-up imaging but the findings were considered to be clinically consistent with posterior circulation ischemic stroke, and 1 patient who had initially presented with posterior circulation symptoms later received a diagnosis of basal ganglia infarction.

EFFICACY OUTCOMES

Functional independence (defined as a score of 0 to 2 on the modified Rankin scale) at 90 days

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Alteplase (N=117)	Standard Treatment (N=117)
Median age (IQR) — yr	64 (57–76)	63 (55–74)
Male sex — no. (%)	75 (64.1)	78 (66.7)
Medical history — no. (%)		
Hypertension	83 (70.9)	73 (62.4)
Diabetes mellitus	40 (34.2)	38 (32.5)
Atrial fibrillation	9 (7.7)	14 (12.0)
Previous ischemic stroke	18 (15.4)	12 (10.3)
Score on the modified Rankin scale before stroke — no. (%)†		
0	114 (97.4)	114 (97.4)
1	3 (2.6)	3 (2.6)
Median NIHSS score at randomization (IQR)‡	3 (2–6)	3 (1–6)
Median PC-ASPECTS at randomization (IQR)§	9 (8–10)	9 (8–10)
Time from stroke onset to randomization — no. (%)		
>4.5 to <9 hr	26 (22.2)	30 (25.6)
9 to 24 hr	41 (35.0)	42 (35.9)
Unknown onset time¶	50 (42.7)	45 (38.5)

* IQR denotes interquartile range.
† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. A score of 0 indicates no symptoms (no neurologic deficit), 1 no significant disability (patients are able to perform all usual activities), 2 slight disability (patients are able to manage personal affairs without help but are unable to perform all previous activities), 3 moderate disability (patients require some help but are able to walk unassisted), 4 moderately severe disability (patients are unable to attend to their own bodily needs without assistance), 5 severe disability (patients require constant nursing care and attention), and 6 death. The prestroke score was determined by inquiring with the patient or the legal representative about the patient's ability to perform activities of daily living before hospitalization for the stroke.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficit.
§ Posterior circulation Acute Stroke Prognosis Early CT Scores (PC-ASPECTS) range from 0 to 10, with lower scores indicating more extensive infarction.
¶ For patients with stroke symptoms of unknown onset time, the onset time was estimated as the midpoint of the time between when the patient was last known to be well and when the patient was found to have symptoms; these patients underwent randomization if the estimated time of onset was within 24 hours.

(the primary outcome) was observed in 89.6% of the patients in the alteplase group and in 72.6% of those in the standard treatment group (unadjusted risk ratio, 1.23; 95% confidence interval [CI], 1.08 to 1.40; P=0.001; adjusted risk ratio, 1.16; 95% CI, 1.03 to 1.30; P=0.01) (Fig. 1 and Table 2). The results for secondary outcomes are shown in Table 2. The percentage of patients with no disability (defined as a score of 0 or 1 on the modified Rankin scale) at 90 days was 73.9% in the alteplase group and 60.7% in the standard treatment group (adjusted risk ratio, 1.16; 95% CI, 0.98 to 1.36). An ordinal analysis of the distribution of scores on the modified Rankin scale showed functional improvement with an adjusted common odds ratio of 2.12 (95% CI, 1.31 to 3.43), favoring alteplase.

Subgroup analyses of the effect of alteplase on the primary outcome are shown in Figure 2. Post hoc analyses of functional outcomes adjusted for age, NIHSS score at randomization, and time from stroke onset to randomization are provided in Table S3. The results for the primary and secondary efficacy outcomes and subgroup analyses in the per-protocol analysis were similar to those of the main analysis (Figs. S3 and S4 and Table S4).

SAFETY OUTCOMES

Symptomatic intracranial hemorrhage within 36 hours after randomization occurred in 2 patients (1.7%) in the alteplase group and in 1 patient (0.9%) in the standard treatment group (unadjusted risk ratio, 1.98; 95% CI, 0.18 to 21.56) (Table 2).

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Parenchymal hematoma was reported in 3 patients (2.6%) in the alteplase group and in 1 patient (0.9%) in the standard treatment group (unadjusted risk ratio, 2.97; 95% CI, 0.31 to 28.17). Mortality at 90 days was 5.2% in the alteplase group and 8.5% in the standard treatment group (unadjusted risk ratio, 0.61; 95% CI, 0.23 to 1.62). Post hoc descriptive presentation of hemorrhagic transformation subtypes on the basis of the Heidelberg classification is shown in Table S5.[16] Details regarding the incidences of other adverse events and serious adverse events are provided in Tables S6 and S7.

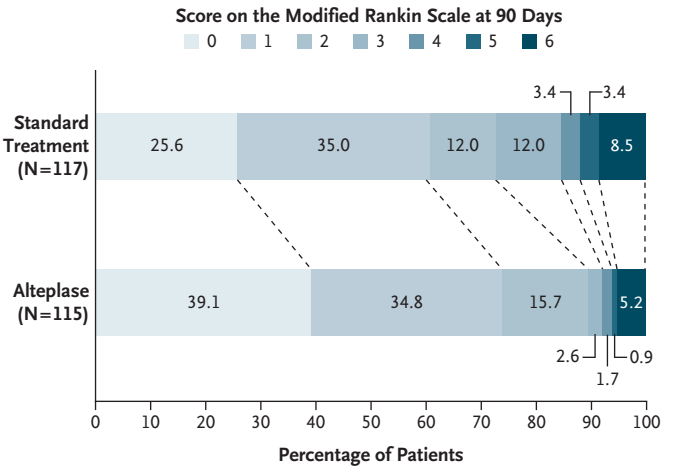

Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

The intention-to-treat population included all the patients who had undergone randomization and for whom outcomes could be assessed. Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. A score of 0 indicates no symptoms (no neurologic deficit), 1 no significant disability (patients are able to perform all usual activities), 2 slight disability (patients are able to manage personal affairs without help but are unable to perform all previous activities), 3 moderate disability (patients require some help but are able to walk unassisted), 4 moderately severe disability (patients are unable to attend to their own bodily needs without assistance), 5 severe disability (patients require constant nursing care and attention), and 6 death. Percentages may not total 100 because of rounding.

DISCUSSION

In this trial involving patients with mostly mild posterior circulation stroke who did not have endovascular thrombectomy planned, functional independence (a score of 0 to 2 on the modified Rankin scale) at 90 days was observed in a higher percentage of patients who received alteplase between 4.5 and 24 hours after stroke onset than in those who received standard medical care. The incidence of symptomatic intracranial hemorrhage within the first 36 hours was similar in the two groups.

The current evidence for extended-window IVT largely focuses on anterior circulation stroke with large-vessel occlusion and usually requires perfusion imaging.[2,4,5,17] However, evidence for extending the thrombolysis window in posterior circulation stroke is lacking, and our trial addresses this gap. In China, intravenous thrombolytic agents have become more widespread with stroke center development, but limited access to perfusion imaging tools and software constrains the use of extended-window thrombolysis. Moreover, the lack of validated perfusion parameters and thresholds for posterior circulation strokes poses additional challenges. This trial explored late-window thrombolysis without the use of perfusion imaging for patient selection, leveraging the lower hemorrhagic risk in posterior circulation strokes to broaden the therapeutic window. Our criteria for diagnosing posterior circulation stroke confirmed the feasibility of identifying and treating these cases in emergency settings and provide a basis for future trials focusing on posterior circulation.

Although tenecteplase is increasingly being adopted in acute stroke management because of its simplified administration and potential benefits, at the time of the trial initiation, there was limited evidence supporting the noninferiority of tenecteplase to alteplase in the Chinese population. Consequently, alteplase was selected on the basis of its established efficacy. Given the promising results with tenecteplase in randomized controlled trials,[4,5] future studies should explore the use of tenecteplase in this specific patient population and refine treatment strategies further.

Our trial has limitations. First, at the time of protocol design, there was no robust evidence supporting the benefit of thrombectomy in basilar-artery occlusion. Patients were excluded if they had thrombectomy planned; these patients typically have more severe symptoms, so the exclusion of these patients resulted in lower overall NIHSS scores and better functional outcomes among the patients in the trial. Consequently, the trial population primarily included patients with mild strokes; therefore, our findings may not be generalizable to patients with

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Table 2. Efficacy and Safety Outcomes.

Outcome	Alteplase (N=117)	Standard Treatment (N=117)	Treatment Effect (95% CI)*
	no./total no. (%)		
Primary outcome			
Score of 0 to 2 on the modified Rankin scale at 90 days	103/115 (89.6)	85/117 (72.6)	1.16 (1.03–1.30)
Secondary outcomes			
Ordinal distribution of the scores on the modified Rankin scale at 90 days			2.12 (1.31–3.43)
0	45/115 (39.1)	30/117 (25.6)	
1	40/115 (34.8)	41/117 (35.0)	
2	18/115 (15.7)	14/117 (12.0)	
3	3/115 (2.6)	14/117 (12.0)	
4	2/115 (1.7)	4/117 (3.4)	
5	1/115 (0.9)	4/117 (3.4)	
6	6/115 (5.2)	10/117 (8.5)	
Score of 0 or 1 on the modified Rankin scale at 90 days	85/115 (73.9)	71/117 (60.7)	1.16 (0.98–1.36)
Major neurologic improvement at 24 hr†	42/116 (36.2)	42/117 (35.9)	0.97 (0.69–1.37)
Major neurologic improvement at 7 days†	65/116 (56.0)	55/113 (48.7)	1.11 (0.87–1.42)
Safety outcomes			
Death within 90 days	6/115 (5.2)	10/117 (8.5)	0.61 (0.23–1.62)
Symptomatic intracranial hemorrhage within 36 hr after randomization‡	2/116 (1.7)	1/115 (0.9)	1.98 (0.18–21.56)
Parenchymal hematoma within 36 hr after randomization§	3/116 (2.6)	1/115 (0.9)	2.97 (0.31–28.17)
Any intracranial hemorrhage within 36 hr after randomization	11/116 (9.5)	5/115 (4.3)	2.18 (0.78–6.08)

* Treatment effects are reported as adjusted risk ratios with 95% confidence intervals for all outcomes, except for the ordinal distribution of scores on the modified Rankin scale, which is reported as an adjusted common odds ratio. Adjustments were made for minimization factors, including age (<65 years or ≥65 years), NIHSS score at randomization (<10 or ≥10), and time from stroke onset to randomization (<9 hours or ≥9 hours). Outcomes for death and intracranial hemorrhage are presented as unadjusted values because of the low number of events. The 95% confidence intervals for the secondary outcomes were not adjusted for multiple comparisons, and no definitive conclusions can be drawn from these data.

† Major neurologic improvement was defined as a reduction of at least 8 points from the baseline NIHSS score or an NIHSS score of 1 or lower. A total of 25 patients at 24 hours and 17 patients at 7 days had both baseline and follow-up NIHSS scores of 1, which met the definition of major neurologic improvement; reclassifying these patients as not having had major neurologic improvement yielded an adjusted risk ratio of 1.18 (95% CI, 0.76 to 1.85) at 24 hours and 1.17 (95% CI, 0.87 to 1.55) at 7 days.

‡ Symptomatic intracranial hemorrhage was defined according to the European Cooperative Acute Stroke Study (ECASS) III criteria[14] as any hemorrhage visible on computed tomographic or magnetic resonance imaging that was associated with clinical deterioration, reflected by an increase in the score on the NIHSS of 4 or more points from baseline, or that lead to death and was identified as the predominant cause of neurologic worsening.

§ Parenchymal hematoma was defined according to the ECASS III criteria[15] as a type of hemorrhagic transformation characterized by a blood clot within the infarcted brain tissue, occupying a substantial portion of the infarct with associated mass effect.

moderate or severe strokes. Second, the trial was open label, which may have influenced the differences in crossover rates, although outcomes were evaluated by clinicians who were unaware of the treatment assignments. Third, the enrolled population predominantly represented the Han Chinese population, so the generalizability of the results to other populations may be limited owing to the differences in stroke mechanisms. In addition, there was some imbalance in stroke mechanisms between trial groups, with a slightly lower proportion of large-artery atherosclerosis in the alteplase group than in the standard treatment group. Finally, in some cases, the diagnosis of

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posterior circulation stroke relied on noncontrast CT and clinical features, and information on the status and location of vascular occlusion was unavailable. This approach theoretically could have resulted in the inclusion of patients with symptoms that mimic stroke and introduced variability in clinical decision making.

In this trial involving Chinese patients with posterior circulation stroke without extensive infarction, with or without large-vessel occlusion, alteplase administered between 4.5 and 24 hours after the onset of stroke was associated with a higher incidence of functional independence at 90 days than standard medical treatment. The incidence of intracranial hemorrhage was similar in the two trial groups. These results support the use of alteplase in this extended time window if endovascular thrombectomy is not available.

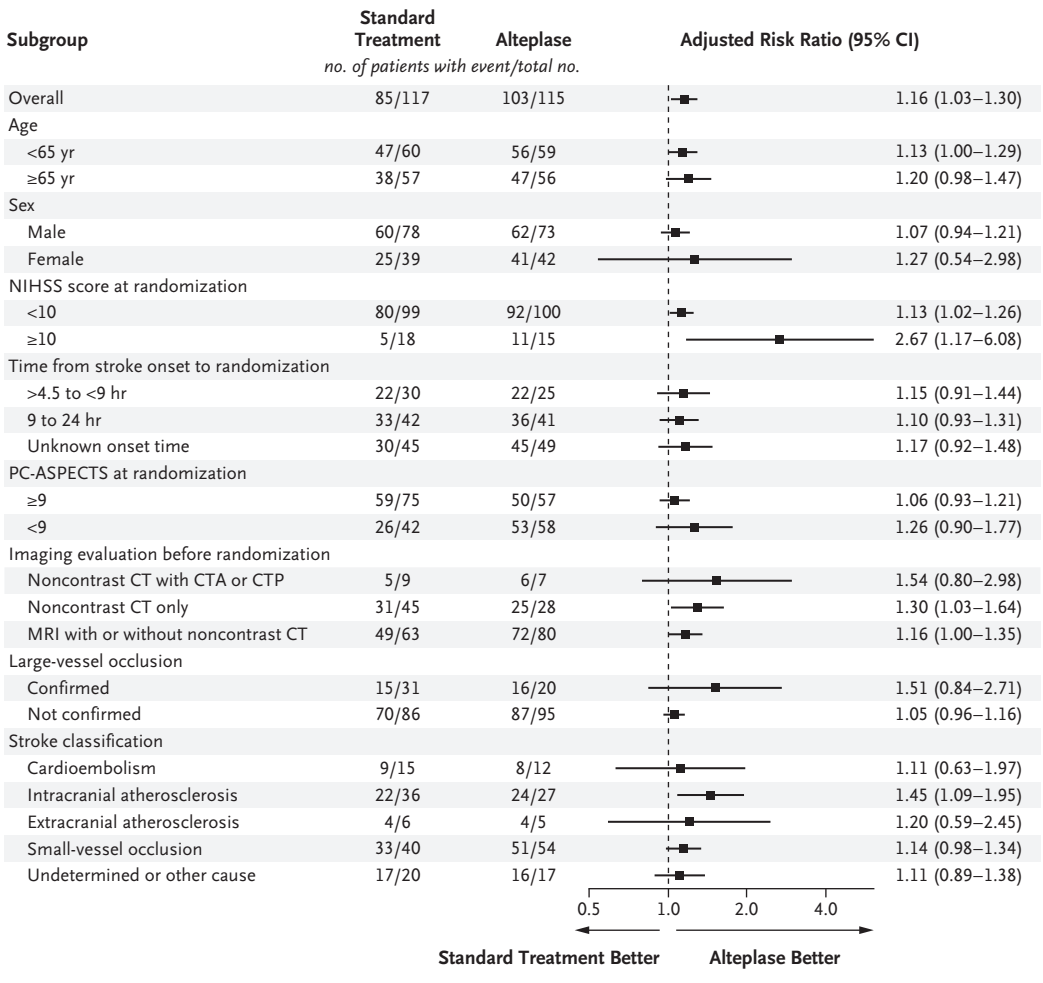
Subgroup
Standard Treatment
Alteplase
Adjusted Risk Ratio (95% CI)
no. of patients with event/total no.
Overall 85/117 103/115 1.16 (1.03–1.30)
Age
<65 yr 47/60 56/59 1.13 (1.00–1.29)
≥65 yr 38/57 47/56 1.20 (0.98–1.47)
Sex
Male 60/78 62/73 1.07 (0.94–1.21)
Female 25/39 41/42 1.27 (0.54–2.98)
NIHSS score at randomization
<10 80/99 92/100 1.13 (1.02–1.26)
≥10 5/18 11/15 2.67 (1.17–6.08)
Time from stroke onset to randomization
>4.5 to <9 hr 22/30 22/25 1.15 (0.91–1.44)
9 to 24 hr 33/42 36/41 1.10 (0.93–1.31)
Unknown onset time 30/45 45/49 1.17 (0.92–1.48)
PC-ASPECTS at randomization
≥9 59/75 50/57 1.06 (0.93–1.21)
<9 26/42 53/58 1.26 (0.90–1.77)
Imaging evaluation before randomization
Noncontrast CT with CTA or CTP 5/9 6/7 1.54 (0.80–2.98)
Noncontrast CT only 31/45 25/28 1.30 (1.03–1.64)
MRI with or without noncontrast CT 49/63 72/80 1.16 (1.00–1.35)
Large-vessel occlusion
Confirmed 15/31 16/20 1.51 (0.84–2.71)
Not confirmed 70/86 87/95 1.05 (0.96–1.16)
Stroke classification
Cardioembolism 9/15 8/12 1.11 (0.63–1.97)
Intracranial atherosclerosis 22/36 24/27 1.45 (1.09–1.95)
Extracranial atherosclerosis 4/6 4/5 1.20 (0.59–2.45)
Small-vessel occlusion 33/40 51/54 1.14 (0.98–1.34)
Undetermined or other cause 17/20 16/17 1.11 (0.89–1.38)
0.5
1.0
2.0
4.0
Standard Treatment Better
Alteplase Better

Figure 2. Subgroup Analyses of the Primary Outcome.

The primary outcome was functional independence (defined as a score of 0 to 2 on the modified Rankin scale) at 90 days. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficit. Posterior circulation Acute Stroke Prognosis Early CT Scores (PC-ASPECTS) range from 0 to 10, with lower scores indicating more extensive infarction. Imaging evaluation before randomization refers to the imaging used to determine patient eligibility at the time of enrollment. Baseline vascular imaging was used to confirm large-vessel occlusion; if baseline imaging was unavailable, follow-up imaging was used for confirmation. Outcomes for imaging evaluation before randomization and stroke classification are reported as unadjusted values owing to the low number of events. In addition, the trial was not sufficiently powered and had no prespecified corrections for multiplicity, preventing a definitive analysis of subgroups. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion, and MRI magnetic resonance imaging.

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